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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,526	04/11/2001	David A. Horwitz	A-68983-1/RFT/RMS/RMK	2496
7590	02/25/2002			

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EXAMINER

HUYNH, PHUONG N

ART UNIT

1644

PAPER NUMBER

6

DATE MAILED: 02/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/833,526

Applicant(s)

HORWITZ, DAVID A.

Examiner

"Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on ____.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-4 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
 5) Claim(s) ____ is/are allowed.
 6) Claim(s) 1-4 is/are rejected.
 7) Claim(s) ____ is/are objected to.
 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 08/28/01 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 11) The proposed drawing correction filed on ____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. ____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.

4) Interview Summary (PTO-413) Paper No(s) ____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: ____.

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DETAILED ACTION

1. Claims 1-4 are pending.
2. Claims 1-4 are being acted upon.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for inducing T cell tolerance ex vivo in peripheral blood mononuclear cells comprising adding a regulatory composition to activate suppressor CD4+ T cells that suppress cytotoxic T cell activity wherein said regulatory composition comprises irradiated mononuclear cells from donor and TGF- β ; (2) a method for inducing a recipients' cells irradiated graft rejection comprising: a) isolating peripheral mononuclear CD4+ cells from a recipient and a donor, b) mixing donor and recipient cells ex vivo, c) treating said cells with a regulatory composition wherein said regulatory composition comprises irradiated mononuclear cells from donor and TGF- β ; d) expanding the number of suppressor CD4+ cells; and e) introducing said suppressor cells to said recipient; (3) the methods mentioned above further comprises cytokine selected from the group consisting of IL-2 and IL-15, does not reasonably provide enablement for (1) a method for inducing T cell tolerance ex vivo in peripheral blood mononuclear cells (PBMCs) comprising adding *any* regulatory composition to activate said cells, (2) a method for inducing a recipient's cells to decrease graft rejection comprising a) isolating peripheral mononuclear blood cells from a recipient and a donor; b) mixing donor and recipient cells ex vivo; c) treating said cells with *any* regulatory composition; d) expanding said cells; and e) introducing said cells to said recipient, (3) a method according to claim 1 or 2 wherein said regulatory composition comprises *any* stimulatory cells and TGF- β and further comprises cytokines selected from the group consisting of IL-2 and IL-15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for inducing T cell tolerance ex vivo by isolating PBMC from both donor and recipient, mixing irradiated T cell-depleted mononuclear cells from donor and CD4+, undifferentiated naïve regulatory T cells from recipient ex vivo, culturing recipient cells with TGF-β and irradiated mononuclear T cells from donors for 3 to 5 days to expand the number of CD4+ suppressor cells and introducing said suppressor cells to the recipient (See page 15 of the specification).

Other than the specific regulatory composition mentioned above for inducing suppressor T cell activity ex vivo, in turn, inducing T cell tolerance and decrease graft rejection upon introducing said suppressor T cell to the recipient, there is insufficient guidance and working examples in the specification as filed about other regulatory composition and stimulator cells that would be useful for a method of inducing T cell tolerance ex vivo and a method for inducing a recipient's cells to decrease graft rejection.

Mysliwetz *et al* teach ex vivo treatment of donor cells with a regulatory composition such as rat IgG2b anti-mouse CD3 MoAb (17A2) fails to induce T cell tolerance and suppress graft rejection such as GVHD (See abstract, in particular). Given the indefinite number of undisclosed regulatory composition and stimulator cells, it is unpredictable to determine which undisclosed regulatory composition and stimulator cells will have the same suppressor T cell activity, in turn, for a method of inducing T cell tolerance and decrease graft rejection.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

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5. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for inducing T cell tolerance *ex vivo* in peripheral blood mononuclear cells (PBMCs) comprising adding *any* regulatory composition to activate said cells wherein said regulatory composition comprises *any* stimulator cells and TGF- β and further comprises cytokines selected from the group consisting of IL-2 and IL-15, (2) a method for inducing a recipient's cells to decrease graft rejection comprising (a) isolating peripheral mononuclear blood cells from a recipient and a donor, (b) mixing donor and recipient cells *ex vivo*; (c) treating cells with *any* regulatory composition; (d) expanding said cells; (e) introducing said cells to said wherein the regulatory composition comprises any stimulator cells and TGF- β and further comprises cytokines selected from the group consisting of IL-2 and IL-15.

The specification discloses only a method for inducing T cell tolerance *ex vivo* by isolating PBMC from both donor and recipient, mixing irradiated T cell-depleted mononuclear cells from donor and CD4+, undifferentiated naïve regulatory T cells from recipient *ex vivo*, culturing recipient cells with TGF- β and irradiated mononuclear T cells from donors for 3 to 5 days to expand the number of CD4+ suppressor cells and introducing said suppressor cells to the recipient (See page 15 of the specification).

With the exception of the specific composition comprising TGF- β and irradiated mononuclear cells from donors mentioned above, there is insufficient written description about the structure associated with functions of (1) *any* "regulatory composition" and (2) *any* "stimulator cells".

Given the lack of a written description of *any* "regulatory composition", *any* "stimulator cells", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398. Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

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6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 99/45524 publication (Sept 1999; PTO 892).

The WO 99/48524 publication teaches a method for inducing T cell tolerance *ex vivo* in peripheral blood mononuclear cells (PBMCs) comprising adding a regulatory composition to activate said cells wherein the regulatory composition is TGF- β and irradiated stimulator cells from recipient (See page 18, lines 10-16, See claims of WO99/48524, in particular). The WO 99/48524 publication further teaches a method for inducing a recipient's cells such as CD8+ T cells to decrease graft rejection comprising isolating peripheral mononuclear cells from blood sample of a donor and a recipient, mixing irradiated donor and recipient cells *ex vivo*, treating said cells with a regulatory composition such as TGF- β and irradiated stimulator cells from recipient (See page 18, lines 10-16, See claims of WO99/48524, in particular) and one or more cytokines such as TGF- β and IL-2 (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular). After expanding said cells in culture, the reference cells are transferred to the recipient (See page 24, lines 1-3, see claim 5 of WO99/48524, in particular). Thus, the reference teachings anticipate the claimed invention.

8. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Halverson *et al* (Blood 90(5): 2089-96, Sept 1997; PTO 892).

Halverson *et al* teach a method for inducing T cell tolerance *ex vivo* in peripheral blood mononuclear cells (PBMCs) such as CD8+ T cells comprising adding a regulatory composition such as TGF- β and stimulator cells from untreated volunteers to activate said CD8+ T cells (See page 2090, column 2 Results, in particular). Thus, the reference teachings anticipate the claimed invention.

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9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/45524 publication (Sept 1999, PTO 892) or Halverson *et al* (Blood 90(5): 2089-96, Sept 1997; PTO 892) each in view of Bonig *et al* (Scand J Immunol 50: 612-618, Dec 1999; PTO 892).
The teachings of WO 99/45524 document and Halverson *et al* have been discussed supra.
The claimed invention as recited in claim 4 differs from the references only by the recitation of the regulatory composition further comprises IL-15.

Bonig *et al* teach IL-15 has some functional similarities to IL-2 since they share a common signal transduction pathway (See page 612, column 1, first paragraph, in particular) and addition of TGF- β , which is a potent suppressor of T cell proliferation, to T cell culture in vitro in the presence of IL-15 or IL-2 further inhibits IFN γ production mediated by either IL-15 or IL-2 alone (See page 615, Figs 2C and 2E, Fig 3, Table 1, in particular). Bonig *et al* further teach that addition of TGF- β to IL-2 or IL-15 culture reduces the number of IFN- γ /CD4 $^{++}$ and IFN- γ /CD8 $^{++}$ cells by 50% and reduces cytoplasmic interferon-accumulation equally in CD4 $^{+}$ and CD8 $^{+}$ cells (See Table 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine IL-15 or IL-2 with TGF- β as taught by Bonig *et al* for a method for inducing T cell tolerance *ex vivo* as taught by Halverson *et al* and WO 99/45524 publication or for a method for inducing a recipient's cells to decrease graft rejection as taught by the WO 99/45524 publication.

One having ordinary skill in the art would have been motivated to this because Bonig *et al* teach that a combination of TGF- β and IL-15 or IL-2 further reduces the number of IFN- γ /CD4 $^{++}$ and IFN- γ /CD8 $^{++}$ cells by 50% and reduces cytoplasmic interferon-accumulation equally in CD4 $^{+}$ and CD8 $^{+}$ cells (See Table 1, in particular) wherein said cells are responsible for T cell tolerance or the lack thereof such as anti-tumor activity.

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11. No claim is allowed.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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February 25, 2002

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